What can zebrafish teach us about our survival in the face of mutations?

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Adaptive mechanisms such as activation and use of cryptic splice sites or alternative transcription start sites as well as nonsense-associated alternative splicing and skipped exons maintaining reading frame shore up a sea of mutations expected to cause premature translation termination and loss of function. Credit: Artist: Neta Schwartz.

Not too long ago, biologists would induce mutations in an entire genome,

isolate an organism that displayed a resulting disease or abnormality that they wanted to study, and then work backward to determine which gene was responsible for the defect. This process often took years to yield definitive results.

Now, thanks to the CRISPR/Cas9 genome-editing tool, biologists can target specific genes for mutation and then see how this induced mutation manifests in an organism—tackling the problem from the other direction. But they are finding that the expected physical changes don't always occur.

Why?

New work from Carnegie's Steven Farber and Jennifer Anderson asked exactly that. They looked at how to circumnavigate one kind of resistance to harmful mutations that's found in a vertebrate organism very applicable to humans—in this case, zebrafish.

Sometimes an organism compensates for a mutation in a gene by changing how it regulates the expression of other related genes—a workaround of sorts. Other times, cells skirt errors in the process by which a gene is first transcribed from DNA into RNA and then translated from RNA into a protein to compensate for a mutation. For example, Anderson and her colleagues described cases wherein cells were able to generate RNAs that survived by splicing out a deleterious mutation. These cells would be expected to produce a protein that is missing a small piece.

"The result may not be perfect, but these compensating measures mean that the organisms can get some of the job done with a less-than-perfect protein," Farber said. "These workarounds show that from an evolutionary perspective, we have some pretty robust mechanisms in place to keep surviving despite mutations."

This raises questions about how to best generate mutations in order to understand the genetic basis of disease—to keep the astounding efficiency of modern methods, but find a way to account for some of an organism's own workarounds, which can inhibit scientists' ability to induce a deleterious mutation.

They find that a good way to hunt out these kinds of genomic workarounds is to look at the RNA phase, which is the intermediary between gene and protein.

"Our work shows that conducting analysis on the RNA level can help us better understand how to not only interpret but also design targeted mutations," Farber added. "We provide guidelines to increase chances that a researcher will disrupt a gene of interest and ultimately characterize its function. This type of basic science approach accelerates the development of diagnostics and therapeutics for a host of human diseases and disorders."

The research team also included Carnegie's Timothy Mulligan and Meng-Chieh Shen, as well as collaborators from the Du (University of Maryland School of Medicine) and Busch-Nentwich (Wellcome Trust Sanger Institute) labs.

The study is published in *PLOS Genetics*.

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